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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,115	FISHER, P.B.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-11,13,14,16-19,21,23,24,26-29,31,33,34,36-39,41 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-11,13,14,16-19,21,23,24,26-29,31,33,34,36-39,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/03;11/04;4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/25/2005 has been entered.

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statements (IDS) submitted 11/23/2004 and 4/25/2005 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements filed 11/23/2004, 4/25/2005 as well as the information disclosure statements filed on 12/3/2001, 12/17/2001, 12/8/2003 have been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass nucleic acid encoding MDA-7 protein. The specification indicates:

> "The term 'MDA-7' as used herein refers to a protein having essentially the amino acid sequence set forth as SEQ ID NO: 2, having Genbank Accession Number U16261. A nucleic acid encoding MDA-7 may have the coding sequence as set forth in SEQ ID NO: 1, Genbank Accession No. U16261, or another sequence which, when translated, produces a protein having essentially the same amino acid sequence. It should be noted that the portion of the nucleic acid sequence presented as SEQ ID NO: 1 which constitutes the protein encoding region extends from nucleotide 275 to nucleotide 895. **The scope of the invention embraces functional equivalents of the nucleic acid and protein** which vary in insignificant ways from the native molecules; for example, it includes isolated nucleic acids which hybridize to the nucleic acid sequence set forth as

SEQ ID NO: 1 under stringent hybridization conditions..." (Emphasis added; see page 18, lines 4-15 of the specification).

Therefore, the claims encompass a genus of nucleic acid molecules which encode variants of "MDA-7 protein" wherein the "MDA-7 protein" can be different from the polypeptide disclosed as SEQ ID NO: 2. Considering that the specification clearly indicates that the invention embraces functional equivalents of the nucleic acid and protein including isolated nucleic acids which hybridize to the nucleic acid sequence set forth as SEQ ID NO: 1 under stringent hybridization conditions, the claims encompass a genus of molecules which includes an enormous number of different species molecules.

It is noted that the claims do not require that the nucleic acids possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of molecules that is defined merely by their ability to hybridize to the nucleic acid sequence set forth as SEQ ID NO: 1 under stringent hybridization conditions. There is no indication in specification or prior art which indicates that any nucleic acid sequence other than a nucleic acid sequence encoding SEQ ID NO: 2 has been delivered to a cancer cell having a mutant *ras* gene, or to a pancreatic cancer cell or that any such variant could be used to inhibit proliferation or treat said cancer cells.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only distinguishing

characteristic of the genus of molecules encompassed by the claims disclosed in the specification is that the nucleic acid hybridizes to SEQ ID NO: 1 under stringent hybridization conditions. The specification does not identify any particular portion or critical elements of the nucleic acid molecule or the encoded MDA-7 protein that must be conserved. Therefore, the claims encompass nucleic acid molecules which encode proteins that may have different functions than the MDA-7 polypeptide disclosed as SEQ ID NO: 2, or which may be non-functional variants. Accordingly, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only isolated nucleic acids encoding the amino acid sequence set forth in SEQ ID NO: 2 meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is

reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for inhibiting proliferation of cancer cells wherein said cancer cells comprise a mutated *ras* gene that increases *RAS* activity in the cancer cell, wherein said method comprises directly administering to said cancer cells a composition comprising:
>
> (i) a nucleic acid that encodes and expresses the polypeptide of SEQ ID NO: 2 (MDA-7), and
>
> (ii) an nucleic acid molecule that specifically hybridizes under stringent conditions to a *RAS* nucleic acid molecule and that inhibits translation of *ras*-specific mRNA;

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of inhibiting proliferation in a population of cancer cells (see claims 1, 3, 4, 6-11, 13, 14, 16-19, 21, 23, 24, 26-29, 31, 33, 34, 36-39), as well as methods for "treating" a subject having pancreatic cancer (see claim 41 and 42). Therefore the general nature of the Invention is cancer therapy. Furthermore, the claims encompass administering a nucleic acid that encodes and expresses a therapeutic protein in a cancer cell, as well as administering a nucleic acid molecule that inhibits translation of *ras*-specific mRNA (e.g., antisense-*ras* oligonucleotides, which is the elected species). Therefore, the nature of the claims is more specifically cancer gene therapy, including antisense therapy.

It is noted that the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

As mentioned above, the claims are very broad. The claims encompass methods of "treating" cancer (including inhibiting proliferation in a population of cancer cells) by increasing the amount of MDA-7 protein via introduction of a nucleic acid molecule which encodes MDA-7 into a cancer cell, and decreasing the activity of *RAS* in said cancer cell by introducing a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (e.g., an antisense-*ras* oligonucleotide).

It is noted that the claims do not indicate that the nucleic acids are administered by any particular route of administration; therefore, the claims encompass any route of administration, including general systemic administration of the nucleic acid molecules. Furthermore, the claims encompass administering any nucleic acid molecule that encodes MDA-7 protein wherein the nucleic acid molecule can be any nucleic molecule which hybridizes to the nucleic acid sequence set forth as SEQ ID NO:1 under stringent hybridization conditions, as indicated above.

It is also noted that claims 1, 3, 4, 6-11, 13, 14, 16-19 are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity. As such, these claims encompass any type of cancer that has any *ras* gene mutation which increases *RAS* activity in the cancer cell.

Claims 21, 23, 24, 26-29, 31, 33, 34 and 36-39 are drawn to a method for inhibiting proliferation of a pancreatic cancer cell wherein the pancreatic cancer cell has a mutated K-*ras* gene. It is noted that the claims do not indicate that the mutated K-*ras* gene results in increased *RAS* activity in the pancreatic cancer cell. As such, these claims encompass inhibiting proliferation of panceratic cells that have any mutated K-*ras* gene, including K-*ras* gene mutations that completely inhibit *RAS* activity in the cell.

Claims 41 and 42 are drawn to a method for treating a subject having pancreatic cancer. It is noted that the instant claims do not indicate that the pancreatic cancer cells have any particular gene mutation; therefore, these claims encompass treating any pancretic cancer, inclusing pancreatic cancers that do not have increased *RAS* activity.

The specification does not provide an enabling disclosure for the full scope of the claims for the following reasons: (1) the claims encompass any route of administration, including

systemic delivery of the nucleic acid molecules, (2) the claims encompass administering nucleic acids which encode variants of SEQ ID NO: 1 without providing sufficient guidance to indicate to one of skill in the art which variants would encode a polypeptide that has the desired function and which variants would have a different function or no function at all, and (3) claims 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42 encompass treating or inhibiting the proliferation of pancreatic cancer cells wherein the pancreatic cancer cells can be cells that do not have increased *RAS* activity. It is noted that claims 21, 23, 24, 26-29, 31, 33, 34, 36-39 encompass methods of treating pancreatic cancer cells having a mutated K-*ras* gene and claims 41 and 42 encompass treating any pancreatic cancer; however, claims 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42 do not indicate that the pancreatic cancer cells have increased *RAS* activity. Therefore, claims 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42 encompass treating pancreatic cancer cells that do not have increased *RAS* activity.

The unpredictability of the art and the state of the prior art

The claims encompass methods of inhibiting the proliferation of cancer cells and treating cancer by administering nucleic acid molecules to a subject having the cancer cells wherein the nucleic acids are administered by any route of administration including systemic delivery.

However, at the time of invention, the relevant art recognizes several problems associated with the general systemic administration of nucleic acids to subjects for treating cancer.

For instance, it is well established in the art that delivery is one of the key problems of gene therapy. Anderson (Nature 1998; 392(suppl):25-30, previously cited) teaches,

> "The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The

> human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease." (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410; previously cited) also indicates some of the problems regarding gene therapy in general. Specifically, regarding the obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, Greco (Frontiers in Biosci. 2002; 7:d1516-1524; previously cited) teaches,

> "The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection." (See p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the therapeutic nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate cells.

Therefore, the art, at the time of filing, indicates that administration of nucleic acid molecules by systemic administration is an inefficient, and thus unpredictable, means of administering therapeutic nucleic acid molecules to specific target cells in a subject.

As noted above, the claims encompass methods comprising administering nucleic acid molecules which encode a MDA-7 protein wherein the nucleic acid can be a variant of SEQ ID NO: 1 including variants that are non-functional or have a function different the MDA-7 polypeptide of SEQ ID NO: 2. There is no indication in specification or prior art which indicates

that any nucleic acid sequence other than a nucleic acid sequence encoding SEQ ID NO: 2 has been delivered to a cancer cell having a mutant *ras* gene, or to a pancreatic cancer cell or that any such variant could be used to inhibit proliferation or treat said cancer cells. The specification does not identify any particular domains or critical elements of the nucleic acid molecule or the encoded MDA-7 protein that must be conserved in order for the molecule to have the desired anti-cancer functions. The specification merely identifies the variants by indicating variants include nucleic acid sequences that hybridize to SEQ ID NO: 1 under stringent hybridization conditions (e.g., see page 18 of the specification). Therefore, the variants encompassed by the claims include nucleic acid sequences that encode polypeptide that have a different amino acid sequence than the MDA-7 polypeptide of SEQ ID NO: 2.

The prior art teaches that changing a single amino acid can completely change the function of a polypeptide. For instance, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Additionally, the genus of nucleic acid molecules has the potential of encompassing a coding sequence that comprises a stop codon that would prematurely terminate translation of the encoded polypeptide possibly resulting in a non-functional peptide fragment. Therefore, the claimed genus of nucleic acid molecules has the potential of encoding proteins having many different functions or which are non-functional variants of SEQ ID NO: 2.

Since there is no indication in the specification or prior art that any sequence other than a sequence encoding SEQ ID NO: 2 would encode a polypeptide having the required function, and since there is insufficient guidance provided indicating which variants encompassed by the claims would have the desired function, additional experimentation would be required to identify the molecules encompassed by the claims which have the desired function. Since the specification does not provide a limiting definition for "stringent" hybridization conditions, and considering that one of skill in the art would recognize that there are "low" as well as "high" stringency conditions, the claims encompass any nucleic acid which would hybridize to SEQ ID NO: 1 under any conditions. Therefore, the claims encompass an enormous number of different variants such that the amount of additional experimentation required to practice the claimed invention to its full scope is undue.

Furthermore, the specification does not provide an enabling disclosure for the embodiments of the claims encompassing methods of treating or inhibiting the proliferation of cancer cells wherein the cancer cells can be cancer cells that do not have increased *RAS* activity (e.g., see claims 21, 23, 24, 26-29, 31, 33, 34, 36-39, 41 and 42). Specifically, the indicated claims encompass administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule (claims 21, 23, 24, 26-29, 31, 33, 34, 36-39 and 41) or an antisense-*ras* oligonucleotide (claim 42); however, the prior art teaches that the nucleic acid molecules that inhibit translation of *ras*-specific mRNA (such as *ras* antisense oligonucleotides) do not inhibit proliferation of cancer cells that do not have increased *RAS* activity.

For instance, Sakakura et al., (Anti-Cancer Drugs, 1995 6:553-561; cited by Applicants in the IDS filed 12/3/2001) teaches that antisense-*ras* oligonucleotides (i.e., nucleic acid molecules

that hybridize under stringent conditions to a *RAS* nucleic acid molecule and inhibit translation of *ras*-specific mRNA) can be used to inhibit the proliferation of a several different colon cancer cell lines having a mutation in one Ki-ras allele. Specifically, Sakakura teaches that the antisense-*ras* oligonucleotide can inhibit the growth of cancer cells, including DLD-1, HCT-116, SW1116 and WiDr cancer cells, having a point mutation in a Ki-ras allele that results in activated RAS (i.e., increased RAS activity) (e.g., see page 553, second column; page 557, Figure 3; page 558, Figure 4 and Table 1; page 559, Table 2). However, difference in the effect of the antisense-ras oligonucleotides compared to controls on the growth rate of cancer cells that do not have a Ki-ras mutation (i.e., COLO 201, WEHI-3 and WI-38 cancer cells) was not statistically significant (see page 557, Figure 3; page 558, Figure 4 and Table 1; page 559, Table 2). Therefore, Sakakura indicates that antisense-*ras* oligonucleotides do not inhibit the growth of cancer cells that do not have an increased *RAS* activity. Furthermore, no examples in the specification or prior could be found which indicates that a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule (such as an antisense-*ras* oligonucleotide) can inhibit the proliferation of a cancer cell that does not have a mutation in a *ras* gene that results in increased *RAS* activity.

Working Examples and Guidance in the Specification

The specification discloses working examples that indicate the administration of a combination of an adenoviral vector that encodes and expresses SEQ ID NO: 2 (MDA-7) and an antisense nucleic acid that specifically hybridizes to a nucleic acid encoding a mutant *ras* mRNA, synergistically inhibited the growth of human pancreatic carcinoma cells having a Ki-ras

mutation that results in increased RAS activity in the cells when the composition was directly administered to these specific cancer cells (e.g., see Figures 5 and 6). The effect was seen only in pancreatic cancer cells that had a mutant K-*ras* gene (not in any other pancreatic cancer cell line). The effect of the combination treatment on pancreatic cancer cells is synergistic because the effect of the combination is greater than the sum of both treatments individually (See Figures 5-6). Several different antisense molecules were tested, including antisense molecules that specifically hybridized to K-ras as well as "scrambled" and "mismatched" antisense sequences; however, only the antisense molecules specific for mutant K-ras mRNA demonstrated the anti-cancer effect. The anti-cancer effect of the combination was demonstrated in cancer cell lines (in vitro) as well as in tumors in mice (wherein the composition was administered directly to the tumors).

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Quantity of Experimentation

Considering the breadth of the claims, an additional experimentation would have to be performed in order for one of skill in the art to be able to practice the invention to the full scope encompassed by the claims. For instance, additional experimentation would be required with respect to the genus of nucleic acid molecules encoding MDA-7 encompassed by the claims, but not adequately described. Further experimentation would be required to overcome the art-recognized problems associated with systemic administration of nucleic acids for cancer therapy. And finally, additional experimentation would be required in order to show that the methods could be used to inhibit the proliferation of cancer cells that do not have increased *RAS* activity,

(such pancreatic cancers that do not have increased *RAS* activity). Considering the problems recognized in the art at the time of filing with respect to systemic administration of nucleic acid molecules, the enormous number of different nucleic acid molecules which encode MDA-7 protein encompassed by the claims, and the teaching in the prior art that antisense-*ras* oligonucleotides do not inhibit the growth of cancer cells that do not have increased *RAS* activity, it is clear that the additional experimentation required to practice broadly claimed invention to its full scope is not routine. Therefore the amount of additional experimentation required is deemed to be undue.

Conclusion

Considering the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited working examples and guidance in the specification, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention to its full scope is undue.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 8, 10, 11, 13, 14 and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes MDA-7 protein and a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patently distinct from the reference

claims(s) because the examined claims are either anticipated by, or would have been obvious over, the reference claim(s). See e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d1046, 29 USPQ2d 2010 (Fed. Cir.) 1993).

Here claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 are drawn to a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

The indicated claims of U.S. Patent No. 5,710,137 differ from the instant claims the examined application in that the claims of U.S. Patent No. 5,710,137 fail to disclose that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

However, Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can

be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the indicated claims of U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the oncogenic Ha-ras mRNA with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because the claims of U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137 as well as Figure 6 of Saison-Behmoaras).

MPEP 2144.06, in discussing art recognized equivalence for the same purpose, mentions *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 1, 6, 7, 9, 11, 16, 17 and 19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-17 of U.S.

Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118) and further in view of WO 97/16547 A1 (Roth et al.).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes MDA-7 protein and a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA, wherein the nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule is comprised in a viral vector, and wherein the viral vector further comprises a nucleic acid encoding MDA-7 in expressible form.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patently distinct from the reference claims(s) because the examined claims are either anticipated by, or would have been obvious over, the reference claim(s). See e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d1046, 29 USPQ2d 2010 (Fed. Cir.) 1993).

Here claims 1, 2 and 5-17 of U.S. Patent No. 5,710,137 are drawn to a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid

molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

The indicated claims of U.S. Patent No. 5,710,137 differ from the instant claims the examined application in that the claims of U.S. Patent No. 5,710,137 fail to disclose that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide) or that the method can comprise administering a viral vector comprising a nucleic acid sequence encoding MDA-7 in expressible for as well as a nucleic acid that expresses a nucleic acid that inhibits the translation of a *ras*-specific mRNA.

Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.). Saison-Behmoaras et al. does not teach that the antisense oligonucleotide can be delivered using an adenoviral vector.

Additionally, WO 97/16547 A1 (Roth et al.) teaches the use of an adenoviral vector to deliver and express an antisense oligonucleotide in a cancer cell. Specifically, Roth teaches an adenoviral vector that expresses an antisense-K-ras oligonucleotide wherein the vector can be used to deliver and express the antisense oligonucleotide in a cancer cell (e.g., see abstract; page 4, lines 6-16; the paragraph bridging pages 4-5; Examples 3 and 4, pages 53-55; etc.). Furthermore, Roth explicitly teaches antisense therapy in combination with other gene therapies and indicates that the combination therapy may produce an improved anticancer treatment (see page 44 lines 14-24). Roth also teaches that the expression vector will be an efficient method for delivering a therapeutically effective gene to counteract clinical disease (see page 43, lines 25-29).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the indicated claims of U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the oncogenic Ha-ras mRNA, wherein the antisense-ras oligonucleotide as well as the nucleic acid encoding the MDA-7 protein are delivered to the cancer cells using an adenoviral vector that encodes and expresses both the antisense-ras oligonucleotide and the MDA-7 protein, with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because (1) the claims of U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137 as well as Figure 6 of Saison-Behmoaras); and (2) Roth teaches that antisense therapy

can be used in combination with other therapies including gene therapy and indicates that the viral vector encoding the antisense nucleic acid can further comprise and express other genes of interest (e.g., see page 33, lines 28-31; page 34, lines 2-4; page 39, lines 5-11; and page 44, lines 14-24).

MPEP 2144.06, in discussing art recognized equivalence for the same purpose, mentions *In re Kerkhoven*, wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 8, 10, 11, 13, 14 and 18 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,710,137 in view of Saison-Behmoaras et al. (EMBO J., 1991; 10(5):1111-1118).

The applied reference (U.S. Patent No. 5,710,137) has a common inventor with the instant application. Based upon the publication date of the patent, it constitutes prior art under 35 U.S.C. 102(b). Therefore, this rejection under 35 U.S.C. 103(a) is not subject to exclusion/disqualification under 35 USC 103(c) See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims are drawn to a method for inhibiting proliferation in a population of cancer cells having a *ras* gene mutation which increases *RAS* activity comprising administering a nucleic acid sequence which encodes MDA-7 protein and a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA.

It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras* mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

U.S. Patent No. 5,710,137 teaches a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon,

prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

U.S. Patent No. 5,710,137 does not teach that that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

However, Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene) (e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to modify the method taught by U.S. Patent No. 5,710,137 such that the method further comprised administering an antisense-ras oligonucleotide that inhibits translation of the oncogenic Ha-ras mRNA (as taught by Saison-Behmoaras) with a reasonable expectation of success.

One of skill in the art would have been motivated to combine the references to create claimed invention because the method taught by U.S. Patent No. 5,710,137 and the method taught by Saison-Behmoaras are equivalent methods that that inhibit the proliferation of cancer cells having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137, as well as Figure 6 of Saison-Behmoaras).

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It is noted that the claims encompass inhibiting proliferation in a population of any cancerous cells having the indicated *ras* gene mutation (such as cancerous cells having a Ha-*ras*

mutation) as well as administering a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

U.S. Patent No. 5,710,137 teaches a method comprising introducing a nucleic acid molecule comprising an MDA-7 gene or gene product into a cancer cell (claims 1 and 9), wherein the cancer cell is in a subject and the nucleic acid molecule is introduced into the cancerous cell (claims 2 and 10), wherein the cancerous cell is characterized by presence of a dominant acting oncogene (claims 5), wherein the dominant acting oncogene is Ha-ras (i.e., a mutant *ras* gene that increases *RAS* activity) (claims 6), wherein the nucleic acid is comprised in a vector (claim 7), wherein the vector is an adenovirus vector, adenoassociated virus vector, a retrovirus or a vaccine virus vector (claim 8), wherein the cancer cell is a breast, cervical, colon, prostate, nasopharyngeal, lung, connective tissue, or nervous system cell (claim 11), as well as pharmaceutical a composition comprising said nucleic acid comprising an MDA-7 gene (claims 12-16).

U.S. Patent No. 5,710,137 does not teach that that the method further comprises a nucleic acid molecule that hybridizes under stringent conditions to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (such as an antisense-*ras* oligonucleotide).

Saison-Behmoaras et al. teaches that an antisense-*ras* oligonucleotide which hybridizes to a *RAS* nucleic acid molecule and inhibits translation of *ras*-specific mRNA (specifically and antisense-Ha-*ras* oligonucleotide that inhibits translation of Ha-*ras* mRNA) can be used to inhibit the proliferation of cells having a mutant Ha-*ras* gene (i.e., an oncogenic Ha-ras gene)

(e.g., see p. 1111, abstract; p. 1116, first column of text and Figure 6; etc.). Saison-Behmoaras et al. does not teach that the antisense oligonucleotide can be delivered using an adenoviral vector.

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having a oncogenic Ha-ras gene that increases RAS activity (e.g., see Figure 1 of U.S. Patent 5,710,137 as well as Figure 6 of Saison-Behmoaras); and (2) Roth teaches that antisense therapy can be used in combination with other therapies including gene therapy and indicates that the viral vector encoding the antisense nucleic acid can further comprise and express other genes of interest (e.g., see page 33, lines 28-31; page 34, lines 2-4; page 39, lines 5-11; and page 44, lines 14-24).

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Response to Arguments

Applicant's arguments filed 4/25/2005 (see pages 10-17) have been fully considered.

With respect to the objection to claims 10, 21-24, and 41, the amendment and applicants arguments are sufficient to overcome the objection. Therefore, the objection is withdrawn.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (written description), the amendment and applicants' arguments are sufficient to overcome the rejection. Therefore, the instant rejection is withdrawn. However, upon further consideration, a new

ground(s) of rejection is made in view of insufficient description of the nucleic acid molecules encoding the MDA-7 protein for the reasons indicated above.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (enablement), applicants' arguments have been fully considered. First, with respect to the rejection as it pertains to "treating" cancer, it is acknowledged that the pending claims are drawn to methods of inhibiting proliferation in a population of cancer cells as well as method of "treating a subject having pancreatic cancer". Since the "treating" claims specifically indicate that the subject has pancreatic cancer and in view of the Applicants' arguments, the rejection as it pertains to prevention of cancer is withdrawn. However, the instant rejection as it pertains to the method of delivery, applicants arguments have been fully considered but are not persuasive.

The Applicant asserts that it would be clear to one of ordinary skill in the art to utilize the instant invention without undue experimentation because the specification and working examples provide sufficient detail to enable the instant invention. The applicants specifically argue that the specification (paragraph (0099) and section 6-9, pages 48-66) disclose the delivery method, alternative routes of delivery and dosage of therapeutic agents and several working examples provided discussing the variables, conditions of treatment, cell culture conditions etc. which fully enable the instant invention. The Applicant also directs The Examiner's attention to Exhibits 1-3 which are references describing the successful utilization of Ad.mda-7 in human clinical trials or to treat systemic disease.

In response, Applicants arguments including Exhibits 1-3 have been fully considered but are not persuasive. With respect to the disclosure of the disclosure of the specification, it is acknowledged that the specification contemplates different routes of administration. However,

the specification does not teach provide any working examples which indicate that the instant claims are enabled for any route of administration other than direct delivery to the cancer cells, in view of the art-recognized problems associated with systemic delivery. With respect to Exhibits 1-3, the Exhibits, it is noted that the Exhibits are post-filing art. It is respectfully pointed out that the specification must provide an enabling disclosure at the time of filing. Furthermore, Exhibits 2 and 3 (Tong et al. and Cunningham et al.) teach a method of inhibiting cancer cell growth by intratumoral injection of an adenoviral vector encoding MDA-7 protein. Therefore Exhibits 2 and 3 are insufficient to overcome the instant rejection. Exhibit 1 (Ramesh et al.) does disclose that local and systemic administration of a nucleic acid encoding MDA-7 protein is sufficient to decrease the growth of primary and metastatic lung tumors in mice wherein the nucleic acid is delivered using DOTAP:cholesterol nanoparticles (e.g., see abstract; page 854 second column; and Figure 5). It is noted with respect to using adenoviral vectors for systemic, Ramesh specifically teaches, "Although these results are encouraging, one limitation of this approach is that its locoregional clinical application-systemic delivery of adenoviruses for treatment of disseminated cancer is not feasible at the present time." Indicating that systemic delivery was not considered feasible as of the date of the reference's publication (2004). Furthermore, the teaching that DOTAP:cholesterol nanoparticles can be used to deliver a nucleic acid encoding a therapeutic gene to cancer cells in vivo by systemic administration appears to be an advancement not recognized in the art at the time the instant application was filed. Furthermore, the instant specification does not appear to contemplate systemic delivery of the therapeutic nucleic acid molecules using DOTAP-cholesterol nanoparticles, which would be

required to overcome the instant rejection. Therefore, Applicants arguments as well as Exhibits 1-3 have been fully considered but do not overcome the instant rejection.

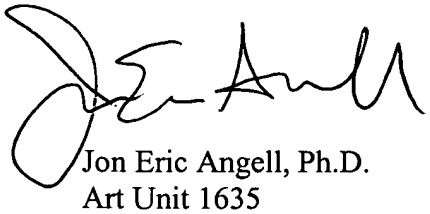
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jon Eric Angell, Ph.D.
Art Unit 1635